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Standardization of Confidence Intervals in PFS Tables - a Macro Approach

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ABSTRACT

Any oncology trial requires time-to-event (TTE) analysis to determine whether an event of interest (EOI) occurred and when it occurred. An EOI can be progression of disease, stable disease, complete remission or death. Usually overall survival (OS) and/or progression-free survival (PFS) tables are requested by statisticians to perform TTE analyses. In this paper, we propose a macro that uses the Proc Lifetest procedure to automate generation of PFS tables and standardize calculation of confidence intervals (CI), in addition to a plethora of other parameters. Usage of Proc Lifetest to generate PFS tables results in consistency. This macro makes calculation of CI much more straight-forward and a standardized process.

INTRODUCTION

This paper will very briefly discuss survival analyses and is mainly intended for statistical programmers in the pharmaceutical industry. **Although the title and abstract focus on CI in PFS tables, scope of the macro is expanded to accommodate other parameters such as survival rate, min, max, 95% CI and 25th-75th percentile in both PFS and OS tables**. Also, with minimal tweaks, this macro can be applied to other TTE analyses. The main objective of this paper is to introduce a macro to standardize calculation of the parameters already mentioned while providing flexibility in how to calculate them. Before discussing our macro approach in detail, let us introduce a few important definitions[1] to familiarize the reader with common TTE analyses in oncology.

- **Progression Free Survival (PFS)**: PFS is the duration of time between randomization, disease diagnosis or start of treatment to clinical disease progression or death. In a clinical trial, measuring PFS is one way to see how well a new treatment works.
- **Overall Survival (OS)**: OS is the length of time from the date of diagnosis, randomization, or the start of treatment to death. In a clinical trial, measuring overall survival is one way to see how well a new treatment works.
- **Event of Interest (EOI)**: An EOI can either be positive or negative. For example, complete remission of disease is considered to be a positive EOI. Similarly, death, progressive disease and recurrence of a disease are considered negative EOIs.
- **Censoring**: Censoring indicates whether a subject experienced an EOI or not. If a subject is censored, then an EOI is not observed and the last time of observation becomes a lower bound for that subject's time to the EOI.

MACRO APPROACH

As we are now familiar with the important parameters, let us discuss the macro. Usually statistical programmers resort to PROC LIFETEST[2] to perform survival analysis and to generate Kaplan–Meier plots. We use PROC LIFETEST in our macro approach as well. This macro provides flexibility in choosing transformation types, confidence bands and time interval etc. In this way, the output dataset from this macro will have all the necessary parameters calculated as required.

The macro was developed keeping in mind that it should be simple and flexible enough for any programmer to incorporate it in their programs. However, to use this macro, programmers need to understand their requirements well and also the desired output layout. All the parameters in the macro call are required to force the programmers to understand all the parameters involved thoroughly.

Below is a sample PFS table layout. The macro presented in this paper generates a dataset with all the parameters needed to create a summary table such as Table 1. The generation of a dataset instead of an RTF file allows for flexible layout from study to study, while standardizing the parameters calculation.

Table 1. Sample Summary of Progression-Free Survival (PFS) table

Table 1: Summary of Progression-Free Survival (PFS) per Investigator
Efficacy Analysis Set

	1 mg/kg (N=6) n (%)	2 mg/kg (N=13) n (%)	3 mg/kg (N=6) n (%)	Total (N=25) n (%)
Number of patients with PD or Death, n (%)	0	2 (15)	0	2 (8)
Estimated Progression-free Rate[a] at:				
3 months (95% C.I.)	100% (100%,100%)	100% (100%,100%)	100% (100%,100%)	100% (100%,100%)
6 months (95% C.I.)	100% (100%,100%)	91% (74%,100%)	100% (100%,100%)	95% (87%,100%)
9 months (95% C.I.)	100% (100%,100%)	91% (74%,100%)	100% (100%,100%)	95% (87%,100%)
12 months (95% C.I.)	100% (100%,100%)	73% (38%,100%)	100% (100%,100%)	85% (64%,100%)
Progression-free survival (Weeks)				
n	6	13	6	25
Median	-	-	-	-
95% CI[b]	-, -	39.9, -	-, -	39.9, -
25th-75th Percentile	-,-	39.9,-	-,-	-,-
Min, Max	25+,48.7+	0.1+,47.9+	8.6+,43+	0.1+,48.7+

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a Denominator is number of subjects with an event
b Computed using the method of Brookmeyer and Crowley

CALLING THE %CI MACRO

The macro has many macro parameters to tailor the output as required. A sample macro call will be as below.

```
%mcrconfintval
( inds = in_pfsds
, outds = out_pfsds
, surv_type = PFS
, timing_variable = PFSM
, censor_variable =cenvarn
, censor_value = 1
, groupvar = dxdiagn
, alpha = .05
, conftype = loglog
, bandtype =all
, tl_min = 3
, tl_max = 24
, tl_div = 3);
```

Required Macro parameters:

- **INDS**: Input dataset
- **OUTDS:** Output dataset
- **ALPHA:** Sets the confidence level for interval estimation estimates
- **SURV_TYPE:** Survival analysis type (only PFS or OS are accepted)
- **CONFTYPE:** Specifies the transformation applied to the survivor function to obtain confidence limits
- **BANDTYPE:** Specifies the type of confidence band in the OUTSURV= data set
- **TL_MIN:** Estimated progression free/Overall survival rate at month (lower limit)
- **TL_MAX:** Estimated progression free/Overall survival rate at month (upper limit)
- **TL_DIV:** Estimated progression free/Overall survival rate at month (division)
- **GROUPVAR:** Grouping / strata variable (example: Male/Female, Adult/Pediatric etc.)
- **Timing_variable:** Progression-free survival/Overall survival in months (Number)
- **Censor_variable:** Censor variable that indicates if PD or Death event occurred
- **Censor_value:** Censor value that indicates if an event occurred

Please note that groupvar, timing_varaible, censor_variable and censor_value variables must be in numeric format.

SAMPLE OUTPUT

A sample output dataset from the macro is as below. It will have confidence intervals and time intervals calculated and ordered.

Output 1 below shows an example of the SAS dataset output from macro.

ROWHEAD1	ROWHEAD2	V1	V2	V98	V999
Number of subjects with PD or Death, n (%)		13 (68)	6 (55)	1 (50)	20 (63)
Estimated Progression-free survival Rate at:	3 months (95% C.I.)	83% (57%,94%)	90% (47%,99%)	100% (-,-)	87% (68%,95%)
Estimated Progression-free survival Rate at:	6 months (95% C.I.)	66% (40%,83%)	79% (38%,94%)	0% (-,-)	68% (48%,82%)
Estimated Progression-free survival Rate at:	9 months (95% C.I.)	66% (40%,83%)	66% (26%,88%)	0% (-,-)	64% (43%,79%)
Estimated Progression-free survival Rate at:	12 months (95% C.I.)	40% (17%,62%)	53% (17%,79%)	0% (-,-)	43% (23%,61%)
Estimated Progression-free survival Rate at:	15 months (95% C.I.)	24% (6%,47%)	35% (6%,68%)	0% (-,-)	27% (10%,46%)
Estimated Progression-free survival Rate at:	18 months (95% C.I.)	24% (6%,47%)	35% (6%,68%)	0% (-,-)	27% (10%,46%)
Estimated Progression-free survival Rate at:	21 months (95% C.I.)	24% (6%,47%)	18% (1%,52%)	0% (-,-)	18% (4%,39%)
Estimated Progression-free survival Rate at:	24 months (95% C.I.)	24% (6%,47%)	18% (1%,52%)	0% (-,-)	18% (4%,39%)
Progression-free survival (months)	n	19	11	2	32
Progression-free survival (months)	Median	10.5	12.9	4.9	10.5
Progression-free survival (months)	95% CI	4.1, 14.2	1.5,-	-,-	4.9, 14.2
Progression-free survival (months)	25th-75th Percentile	4.1, 14.2	7.9, 18.5	4.9, 4.9	4.6, 18.5
Progression-free survival (months)	Min, Max	1.1+ , -	1.4+ , 29.2+	4.1+ , -	1.1+ , 29.2+

LIMITATIONS

We would like to note that this macro has a limitation. It can only create PFS or OS datasets separately each time. So if the programmer wants to present PFS and OS altogether, the macro has to be called twice.

CONCLUSION

This paper demonstrates how we can standardize the calculation of confidence intervals for PFS and OS tables. This macro allows for a consistent production of PFS or OS tables, more elegant and portable code and better ways to utilize the LIFETEST procedure.

REFERENCES

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